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THE C₄-SACCHARINIC ACIDS

VIII. FURTHER ATTEMPTS TO PREPARE 2,2'-DIHYDROXYISOBUTYRIC ACID. 2,3-DIHYDROXYBUTYRIC ACID LACTONE FROM GLYCIDOL. THE PREPARATION OF THE TWO IODOHYDRINS OF GLYCEROL

A PART OF A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1932

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ROSALIND AMELIA KLAAS

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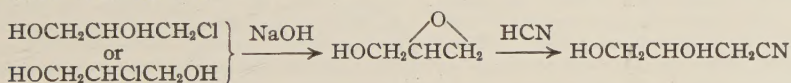
1933



The C₄-Saccharinic Acids. VIII. Further Attempts to Prepare 2,2'-Dihydroxyisobutyric Acid. 2,3-Dihydroxybutyric Acid Lactone from Glycidol. The Preparation of the Two Iodohydrins of Glycerol

In previous work in this Laboratory¹ it was found that 2,2'-dihydroxyisobutyric acid could not be prepared by the treatment of β -glycerol chlorohydrin with sodium cyanide followed by hydrolysis of the nitrile thus obtained. Pure β -glycerol chlorohydrin gave the same product as did pure α -glycerol chlorohydrin, namely, 2,3-dihydroxybutyric acid lactone (hereafter called, for the sake of brevity, "2,3-acid lactone"). In explanation of this fact it was suggested that both chlorohydrins under the experimental conditions used yielded glycidol, which then added hydrogen cyanide to form the nitrile of the 2,3-acid almost exclusively. This paper reports the results of a study which was undertaken partly to test this hypothesis.

The reaction of glycidol with hydrogen cyanide was carried out under various conditions; in each experiment, with one exception, the only product that was isolated and identified was the 2,3-acid lactone, in a yield varying from 25 to 50%. The one exception was an experiment with benzene as the solvent in which the chief product of the reaction was 3-hydroxyisocrotonic acid lactone.² Other products of the reaction consisted of dark-colored tars, probably polymers of glycidol, and of acids of high molecular weight. The results of the study thus confirm the hypothesis that the mechanism of the reaction of the monochlorohydrins of glycerol with sodium cyanide is as follows:



On the basis of this theory, it is the alkali resulting from the hydrolysis of the cyanide which causes the formation of the glycidol. In the further attempt to prepare 2,2'-dihydroxyisobutyric acid from β -chlorohydrin, the presence of alkali was avoided by the use of cuprous cyanide³ and of mercuric cyanide.⁴ With the former, a small amount of acid of high molecular weight was obtained, while with the latter only tars and resins resulted.

(1) Glattfeld, Leavell, Spieth and Hutton, *J. Am. Chem. Soc.*, **53**, 3164 (1931).

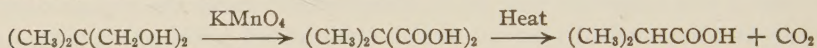
(2) It is interesting to note that 3-hydroxyisocrotonic acid lactone is also formed in the preparation of the 2,3-acid from glycerol chlorohydrin and sodium cyanide in water or alcohol solution.¹ The exact source of this by-product has not yet been ascertained, but in view of the data in the experiment mentioned above, it must be formed at some time after the glycidol is generated from the chlorohydrin.

(3) Tschelinzeff and Schmidt, *Ber.*, **62**, 2211 (1929).

(4) Guillemard, *Ann. chim. phys.*, [8] **14**, 383 (1908); *Bull. soc. chim.*, [4] **1**, 532 (1907).

The diacetyl and dibenzoyl derivatives of β -glycerol chlorohydrin⁵ were also used in the attempt to prepare 2,2'-dihydroxyisobutyric acid, inasmuch as these cannot readily form oxygen ring compounds. It was shown, however, that they are rather inactive substances, for they failed to react with magnesium with ether as the solvent. Even metallic sodium did not remove the chlorine atom from the dibenzoyl compound dissolved in benzene when the mixture was heated for fifteen hours. The diacetyl derivative, on the other hand, was decomposed by sodium. However, the reaction in which the diacetyl compound was treated with ethyl chloroformate and 4% sodium amalgam,⁶ with subsequent hydrolysis of the product formed, failed to yield any acid which could be identified as 2,2'-dihydroxyisobutyric acid.

A few experiments on the oxidation of pentaerythritol were next carried out. Just⁷ was able to obtain isobutyric acid from 2,2-dimethylpropane-1,3-diol (1,3), according to the equation



It was hoped that under suitable conditions an analogous reaction would take place with pentaerythritol which would yield 2,2'-dihydroxyisobutyric acid. Dilute solutions of potassium permanganate and of barium permanganate were employed as oxidizing agents in neutral and in acid media. The reaction was in each case vigorous, even at 5°, but the chief product of the oxidation appeared to be carbon dioxide. These experiments with pentaerythritol are only preliminary, and it is planned to study this reaction further.

Since it was thought that β -glycerol iodohydrin might prove a possible source material for the acid desired, its synthesis was effected. The α -

(5) These compounds were prepared in this Laboratory by G. W. Schimpff (S. M. Dissertation, University of Chicago, 1930). The diacetyl compound was obtained by refluxing 1 mole of pure β -glycerol chlorohydrin ($K_{50} = 0.92$. See Smith, *Z. physik. Chem.*, **92**, 717-740 (1918); **94**, 691-738 (1920)) with 4 moles of acetic anhydride for eight hours, removing the acetic acid and excess anhydride by distillation at atmospheric pressure, and boiling the residue for four hours with 2 moles of acetic anhydride. After the removal of acetic acid and excess anhydride as before, the residue was heated with water in order to remove unchanged β -glycerol chlorohydrin. The aqueous layer was discarded and the residue fractionated. A fraction which boiled at 107-109° at 5-6 mm. with oil-bath at 132-134° was redistilled; it gave a product which boiled at 101-102° at 4 mm. with oil-bath at 114-116°; yield 51%.

Anal. Subs., 0.2528, 0.2528: 12.92 cc., 13.00 cc. of 0.0991 *N* AgNO₃. Calcd. for C₇H₁₁O₄Cl: Cl, 18.23. Found: Cl, 17.96, 18.07.

The dibenzoyl derivative was prepared by mixing at 0° a solution of 1 mole of pure β -glycerol chlorohydrin in 2.5 moles of pyridine with a solution of 2 moles of benzoyl chloride in 6 moles of chloroform. After the mixture had been allowed to stand at room temperature for twenty-four hours, it was shaken with 3 volumes of a mixture of equal volumes of water and ether. The ether extract was washed successively with dilute sulfuric acid, sodium bicarbonate solution, and water, and then dried over anhydrous sodium sulfate. After the removal of the ether, the residue was fractionated. The fraction which distilled at 212-224° at 4 mm. was redistilled; it gave a product which boiled at 210-211° at 1.5 mm.; yield 39%.

Anal. Subs., 0.2868, 0.2907: 9.40 cc., 9.50 cc. of 0.0991 *N* AgNO₃. Calcd. for C₁₇H₁₅O₄Cl: Cl, 11.13. Found: Cl, 11.51, 11.48.

(6) Würtz, *Compt. rend.*, **68**, 1298 (1869). Cf. Calvery, *J. Am. Chem. Soc.*, **48**, 1009 (1926).

(7) Just, *Monatsh.*, **17**, 76 (1896).

glycerol iodohydrin⁸ has been known for some time, but the β -iodo derivative is new to the literature. Since the methods of preparation used by previous workers were long and tedious, a new procedure was developed for the preparation of the alpha compound. The same procedure was then adapted to the preparation of the beta compound. The details are given below.

This paper also reports some work on the reaction of β -iodohydrin with sodium cyanide. The experiments carried out gave rise only to the 2,3-acid and to sirupy materials that were not identified. Thus at the present time the results indicate that β -glycerol iodohydrin, like the β -chlorohydrin, gives the straight chain nitrile after reaction with alkali cyanides.

A method for the preparation of the 2,2'-dihydroxyisobutyric acid is still being sought in this Laboratory.

Experimental Part

Glycidol and Gaseous Hydrogen Cyanide.—Glycidol (boiling point 42–43° at 1.5 mm. with bath at 70°) was prepared from glycerol monochlorohydrin according to the method of Rider and Hill⁹. Anhydrous gaseous hydrogen cyanide was bubbled through 10 g. of glycidol until the gain in weight was 4.5 g. (3.7 g. calcd.). The solution was heated in a pressure bottle at 60–70° for twelve hours. After the excess hydrogen cyanide had been removed at reduced pressure, the sirup was dissolved in 100 cc. of water, and to the solution 21 g. of hydrated barium hydroxide was added. The mixture was heated on a steam-bath for thirty hours under a reflux condenser while a stream of nitrogen was bubbled through. After the removal of all but a trace of the barium ion by means of sulfuric acid and of the water by distillation at reduced pressure, there remained 13.7 g. of a very dark sirup. This was extracted repeatedly with small portions of boiling absolute ethanol in which the tarry material present was insoluble. After the removal of the alcohol at reduced pressure, the residue (weight 9.1 g.) was distilled at 4 mm. The first drop of distillate came at 128° with the bath at 172°, but practically all of the distillate (weight 3.5 g.) came at 140–146° with the bath at 185°. This boiling range and the phenylhydrazide (m. p. 109°) prepared from the acid, identified this material as 2,3-dihydroxybutyric acid lactone; yield, 25%.

Glycidol and a Benzene Solution of Hydrogen Cyanide.—To a solution of 5 g. of liquid hydrogen cyanide and 5 g. of glycidol in 13.5 g. of benzene, there were added a few crystals of potassium cyanide moistened with a drop of water. The mixture was allowed to stand for six days at room temperature. At the end of that time two layers had formed. The upper benzene layer was decanted and gentle suction was applied to the residue to remove all volatile constituents. The brown viscous sirup which remained was dissolved in 60 cc. of water, and 6 g. of anhydrous barium hydroxide added. The mixture was heated on the steam-bath under a reflux condenser in a stream of nitrogen until no more ammonia was evolved (forty-two hours). After the removal of the barium ion and of the water, the sirup was distilled at 2 mm. The distillate, which came over between 50 and 110° with the bath at 160–180°, weighed 2.7 g. Upon redistillation, 1.5 g. of a colorless liquid was obtained, which crystallized when chilled in a carbon dioxide-acetone mixture and melted at 2°. After redistillation the boiling point was 71° at 2.5 mm. with the bath at 125° and the melting point 5°. These are the con-

(8) (a) Réboul, *Jahresb. Fortschritte Chem.*, 459 (1860); (b) Lüders, German patent 291,541, 291,922 (1914); cf. *Schweiz. Apoth.-Ztg.*, 53, 613 (1915); (c) Fischer and Pfähler, *Ber.*, 53, 1606 (1920).

(9) Rider and Hill, *J. Am. Chem. Soc.*, 52, 1521 (1930).

stants for 3-hydroxyisocrotonic acid lactone, which is thus shown to be the main product of the reaction under the conditions chosen for this experiment.

Glycidol and an Aqueous Solution of Hydrogen Cyanide.—A 500-cc. three-necked flask, fitted with a reflux condenser, a dropping funnel, and a mercury-sealed mechanical stirrer, was used in this experiment. A few crystals of potassium cyanide were added to a solution of 14.5 g. of liquid hydrogen cyanide in 30 cc. of water. The solution was warmed on the steam-bath to such a temperature that liquid dropped from the end of the condenser at the rate of thirty drops per minute. Twenty grams of glycidol was added with stirring during the course of two and a half hours. The heating and stirring of the solution were continued for three hours longer. After the removal of the excess hydrogen cyanide and part of the water by reduced pressure distillation, the residue was dissolved in 200 cc. of water, and 24 g. of anhydrous barium hydroxide added. The mixture was heated for thirty-six hours on the steam-bath under a reflux condenser in a stream of nitrogen. After the removal of the barium ion and of the water in the usual manner, there remained 28 g. of viscous brown sirup. This was combined with 14.5 g. of sirup similarly prepared from 10 g. of glycidol. The combined material was distilled at 3 mm. A 3-g. fraction was collected from 78 to 130°, and 24.1 g. from 130 to 154°. The residue was a dark glass-like substance, almost insoluble in water. Titration indicated that the larger fraction was 2,3-acid lactone, since it titrated 4.8% free acid and 85.9% lactone.¹⁰ The yield of 2,3-acid lactone calculated on the basis of this analysis was 50%. The lactone was purified by conversion to the barium salt, removal of the barium, and distillation of the lactone. A sample titrated correctly for a dihydroxybutyric lactone (subs., 0.2013; calcd. 19.73 cc. of 0.1 N alkali; found, 19.20 cc.), and it gave a phenylhydrazide which melted at 109°.

Preparation of α -Glycerol Iodohydrin.—This compound was prepared by Lüders^{8b} by shaking α -glycerol chlorohydrin with excess sodium iodide for many days. Fischer and Pfähler^{8c} prepared it from isopropylidene- α -chlorohydrin by dissolving this compound in alcohol and heating it with sodium iodide in a sealed tube at 100° for three days. The method used in the present study was developed from the work done by Conant and Kirner¹¹ on the rate of transformation of chlorides into iodides.

A mixture which consisted of 23 g. of crude (*i. e.*, containing some β -) α -glycerol chlorohydrin (prepared from glycerol and hydrochloric acid), 35 g. of sodium iodide, and 200 cc. of acetone was introduced into each of two citrate of magnesia bottles and heated in steam for four hours. The sodium iodide used was dried in an oven at 110° for two hours and cooled in a desiccator. The acetone was boiled with lime and potassium permanganate for several days and then distilled through a 61-cm. fractionating column. The fraction which boiled at 56–56.5° was collected in a receiver carefully protected from moisture. The sodium chloride was removed from the cooled reaction mixture by suction filtration and washed with acetone until white (wt. 18.5 g., 75%). After the removal of the acetone at reduced pressure at 40°, the sirup was extracted with ether (which had been dried over anhydrous sodium sulfate) until the excess sodium iodide was white and powdery. The ether extracts were decanted, combined, washed with sufficient concentrated sodium thiosulfate solution to remove the iodine, and dried over anhydrous sodium sulfate. After the removal of the ether the residue was distilled. A large fraction (isopropylidene- α -iodohydrin, wt. 36 g., yield 37%) came at 75–78° at 5–6 mm. with the bath at 100–105°; and a 4-g. fraction was collected while the temperature of the bath was raised to 148°, with the temperature of the vapor rising rather rapidly to 115°. Distillation was then stopped, because the flask became filled with iodine vapors. The dark residue (wt. 28 g.), when seeded with a crystal of α -glycerol iodohydrin, set to a mass of crystals. The crystals were pressed between filter papers to

(10) Glattfeld and Miller, *J. Am. Chem. Soc.*, **42**, 2317 (1920).

(11) Conant and Kirner, *ibid.*, **46**, 232 (1924).

remove adhering oils, dissolved in warm chloroform and precipitated with high boiling ligroin; weight 12.5 g., glistening, scale-like crystals, m. p. 47–47.5°, yield 15%. These retained a cream tint even after several recrystallizations.

Pure white crystals were obtained, however, by the hydrolysis of isopropylidene- α -iodohydrin (36 g. fraction above). Into a mixture of this compound (which had been washed with sodium thiosulfate solution and water) with three times its weight of water there was introduced a drop of 5 *N* hydrochloric acid. The mixture was heated with vigorous shaking under a reflux condenser until the globules of oil disappeared. The cold solution was extracted with ether, and the extract dried over anhydrous potassium carbonate. After the evaporation of the ether, the clear viscous sirup set to a solid mass of crystals. In one experiment 28 g. was obtained from 65 g. of isopropylidene- α -iodohydrin. After two recrystallizations from a chloroform–ligroin mixture, the crystals melted at 48–48.5°.

Anal. Subs., 0.1097, 0.1254: 5.49 cc., 6.29 cc. of 0.09973 *N* AgNO₃. Calcd. for C₈H₇O₂I: I, 62.85. Found: I, 63.34, 63.48. This product was identical with that obtained under similar conditions from a sample of pure α -glycerol chlorohydrin (*K*₅₀ = 9.5).

Preparation of β -Glycerol Iodohydrin.—Freshly distilled pure β -glycerol chlorohydrin (*K*₅₀ = 0.605, % Cl = 31.46) was used as the starting material. The procedure described above was used except that the time of heating was prolonged to twelve hours. The weight of sodium chloride that separated was 60% of the theoretical. After the removal of the ether, the residue was fractionated at 2 mm. in order to remove unchanged β -chlorohydrin. The distillation was discontinued when a temperature of 108° was reached, with the bath at 135°. Even though a stream of dry nitrogen was conducted through the apparatus during the distillation, the decomposition was marked. The drop of clear liquid adhering to the thermometer at the end of the distillation was transferred to a watch crystal and stirred. It quickly set to a mass of crystals. These were used to inoculate the dark viscous residue, which almost immediately became a thick crystalline mass. This was pressed on sheets of filter paper to remove the adhering dark oil; 15 g. of cream colored crystals was obtained from 45 g. of β -chlorohydrin, yield 18%. These were dissolved in warm chloroform, and after the solution had cooled to 10°, 11 g. of fine, white needles was obtained; m. p. 52–53°; soluble in water, ethanol, chloroform, acetone, ether; insoluble in ligroin. When a few of the crystals were mixed with crystals of pure α -glycerol iodohydrin, the mixture turned at once to a soft paste. When small amounts of each type of crystals were introduced separately into a melting point tube and mixed by vibrating the tube with a file, the mixture melted from 32 to 45°.

Anal. Subs., 0.1216, 0.0552: 6.13 cc., 2.77 cc. of 0.09973 *N* AgNO₃. Calcd. for C₈H₇O₂I: I, 62.85. Found: I, 63.80, 63.51.

Reaction of β -Iodohydrin with Sodium Cyanide.—Five grams of β -glycerol iodohydrin and 1.21 g. of sodium cyanide were dissolved in a mixture of 25 cc. of 95% ethanol and 4 cc. of water. The solution was heated under a reflux condenser for two hours. It was then acidified with 0.1 *N* nitric acid, and a solution of 4.21 g. of silver nitrate in 50 cc. of water was slowly added. The purpose of this procedure was to replace the sodium iodide by sodium nitrate, which is far less soluble in ethanol than is sodium iodide. The silver iodide was removed by filtration. The water was removed *in vacuo*, and the residue extracted with ethanol. After the removal of the ethanol, the residue was dissolved in 50 cc. of water, and 2.1 g. of anhydrous barium hydroxide added. The mixture was heated on a steam-bath for eighteen hours under a reflux condenser in a stream of nitrogen. After the removal of all but a trace of the barium ion and of the water, there remained a viscous sirup, from which a phenylhydrazide

which melted at 107.5–108.5° was prepared. When some of this material was mixed with crystals of the phenylhydrazide of 2,3-dihydroxybutyric acid (m. p. 109°), no depression in melting point was observed. It thus appears that 2,3-dihydroxybutyric acid had been formed in the reaction of the β -iodohydrin with sodium cyanide.

Summary

1. The addition of hydrogen cyanide to glycidol followed by hydrolysis of the addition product resulted in a 25–50% yield of 2,3-dihydroxybutyric acid lactone. Under certain conditions, 3-hydroxyisocrotonic acid lactone was formed.

2. Further attempts were made to prepare 2,2'-dihydroxyisobutyric acid from (a) β -glycerol chlorohydrin and heavy metal cyanides; (b) β -glycerol chlorohydrin diacetate, ethyl chloroformate and sodium amalgam; and (c) pentaerythritol by oxidation with barium or potassium permanganate. These attempts were unsuccessful.

3. α -Glycerol iodohydrin was prepared by a new procedure.

4. β -Glycerol iodohydrin was prepared and its melting point determined. The reaction of this compound with sodium cyanide in ethanol gave 2,3-dihydroxybutyric acid.

Acknowledgment

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